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09/919,349	07/31/2001	John G. Babish	T8702.NP	2751

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EXAMINER
FLOOD, MICHELE C

ART UNIT	PAPER NUMBER
1654	12

DATE MAILED: 05/01/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.	Applicant(s)
09/919,349	BABISH et al.
Examiner	**Art Unit**
Michele Flood	1654

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) X Responsive to communication(s) filed on *Feb 14, 2003* .

2a) ☐ This action is **FINAL.** 2b) X This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) X Claim(s) *1-42* is/are pending in the application.

4a) Of the above, claim(s) *26-42* is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) X Claim(s) *1-25* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) X Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) X Notice of References Cited (PTO-892)	4) ☐ Interview Summary (PTO-413) Paper No(s).
2) X Notice of Draftsperson's Patent Drawing Review (PTO-948)	5) ☐ Notice of Informal Patent Application (PTO-152)
3) X Information Disclosure Statement(s) (PTO-1449) Paper No(s). 5	6) ☐ Other:

DETAILED ACTION

Election/Restriction

1. Applicant's election without traverse of Group I, Claims 1-25, in Paper No. 11 is acknowledged. Further acknowledgment is made of Applicant's election of the species triptolide as the diterpene triepoxide lactone species, and parthenolide as the sesquiterpene lactone species.

Claims 1-25 are under examination.

The claims have been examined, insofar as they read on the elected specia, namely triptolide as the diterpene triepoxide lactone species, and parthenolide as the sesquiterpene lactone species.

Claim Rejections - 35 USC § 112

2. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-25 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1, 6, 11, 16 and 21 recite the abbreviation "COX". Abbreviations in the first instance of claims should be expanded upon with the abbreviation indicated in parentheses. The abbreviations can be used thereafter.

Claims 1 recites the limitation "derivative". One of ordinary skill in the art would not know how to interpret the metes and bounds of this limitation. A derivation of a chemical compound may be closely patterned after the subject chemical compound or may be loosely patterned after the subject chemical compound, such that it may bear no resemblance or form recognizable as the subject chemical compound which maybe chemically and/or biologically unrelated in function or form to the subject chemical compound.

With regard to Claims 2-5, 7-10, 12-15, 16-20 and 22-25, the capital "C" which appears in "Claim" should be replaced with a lower case c.

The term "minimal effect" in Claims 1, 6, 11, 16 and 21 is a relative term which renders the claim indefinite. The term "minimal effect" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention.

With regard to Claims 5, line 3, there is an apparent misspelling. Applicant may overcome the rejection by replacing "chondrotin" with chondroitin.

With regard to Claims 6, line 6, there is an apparent misspelling. Applicant may overcome the rejection by replacing "melapodin A" with melapomdin A.

All other cited claims depend directly or indirectly from rejected claims and are, therefore, also, rejected under U.S.C. 112, second paragraph for the reasons set forth above.

Claim Rejections - 35 USC § 103

3. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

4. Claims 1-4, 6-9, 11-14, 16-19 and 21-24 are rejected under 35 U.S.C. 103(a) as being unpatentable over Tao et al. (U) in view of Hwang et al. (V).

Applicant's claims a composition for inhibition of inducible COX-2 activity and having minimal effect on COX-1 activity, said composition comprising as a first component an effective amount of a diterpene triepoxide lactone species, and as a second component an effective amount of a sesquiterpene lactone species or derivatives thereof. Applicant further claims the composition of claim 1 wherein the first and second components are derived from plants or plant extracts. Applicant further claims a composition, wherein at least one of said first or second component is conjugated with a compound selected from the group consisting of mono- or di-saccharides, amino acids, sulfates, succinate, acetate and glutathione. Applicant further claims a composition formulated in a pharmaceutically acceptable carrier.

Tao teaches a composition comprising the diterpene triepoxide lactone, triptolide, which is obtained from an ethyl acetate extract of the plant *Tripterygium wilfordii* Hook F (see page 131, Columns 1 and 2, under "MATERIALS AND METHODS"). Tao teaches that the triptolide

inhibited LPS-stimulated induction of COX-2 mRNA and synthesis of prostaglandin E_2 (PGE_2). See Table 1, on page 133. On page 133, Column 2, lines 10-18, Tao teaches, "Triptolide, a major active component that is known to be responsible for the immunosuppressive action of TWHF (*Tripterygium wilfordii* Hook F) on T cells and B cells, potently inhibited PGE_2 production by RASF (RA synovial fibroblasts) and HM (human monocytes), with an IC_{50} of 3.78 ng/ml and 4.52 ng/ml, respectively (Table 1). Triptolide also inhibited PGE_2 production by HFF (human foreskin fibroblasts), but less effectively, with an IC_{50} of 9.42 ng/ml." On page 134, Column 1, lines 7-8 and Column 2, line 1, Tao further teaches that triptolide was inhibitory of COX-2 mRNA expression. In Figure 6 on page 135, Tao shows that a methanol/chloroform (T2) extract of *Tripterygium wilfordii* Hook F "preferentially inhibited the expression of the inducible COX-2 mRNA, but not the constitutive COX-1 mRNA." Finally, Tao teaches that triptolide was more effective at inhibiting production of IL-2 than of PGE_2 (see page 136, lines 5-9; and Table 3). Hwang teaches a composition comprising the sesquiterpene lactone, parthenolide, and other sesquiterpene lactones, which are extracted from the leaves of *Magnolia grandiflora*. See Figure 1. On page 811, lines 28-31, Hwang teaches, "The dose-response to parthenolide in inhibiting the expression of COX activity showed that the IC_{50} is 0.8 μM as shown in Fig. 2. Similar inhibitions of the expression of COX-2 protein and steady state levels of COX-2 mRNA are shown in Fig. 3. Hwang further teaches that parthenolide suppressed LPS-induced TNFα production with an IC_{50} of 0.1 μg/ml (see Fig. 2); inhibited steady state levels of mRNA for TNFα and ILβ (see Fig. 4); and inhibited the expression of IL-1α protein (see Fig. 3). On page 815, lines 10-12, Hwang

teaches, "Among sesquiterpene tested, parthenolide, encelin, and leucanthin B (1, 2, and respectively in Table 1) showed the highest inhibitory activity (i.e., inhibition of COX-2 activity)."

The teachings of Tao and Hwang are set forth above. Tao does not a composition comprising an effective amount of a sesquiterpene lactone, and Hwang does not teach a composition comprising an effective amount of diterpene triepoxide lactone. However, it would have been obvious to one of ordinary skill in the art at the time the invention was made to combine the triptolide taught by Tao with the parthenolide taught by Hwang to provide the claimed composition because Tao and Hwang each teach the beneficial therapeutic effects of their compositions for the inhibition of inducible COX-2 activity and Tao teaches that his composition has minimal effect on COX-1 activity. At the time the invention was made, one of ordinary skill in the art would have been motivated and one would have had a reasonable expectation of success to combine an effective amount of the triptolide (a diterpene triepoxide) with an effective amount of the parthenolide (sesquiterpene lactone) taught by Hwang to provide the claimed invention because Tao suggests that the capacity of the EA extract and T2 to inhibit the expression of COX-2 mRNA but not COX-1 mRNA may explain its marked in vitro antiinflammatory effects and Tao teaches that triptolide exerts more potent inhibitory effects on IL-production by T cells than on PGE_2 production by monocytes; and, Hwang teaches, "Our finding that parthenolide inhibits tyrosine phosphorylation of MAPKs and the production of proinflammatory cytokines, offers a possibility that some of the sesquiterpene lactones can be used as a therapeutic agent for septic shock and other acute inflammatory diseases", on page 817, lines -11. Further motivation

to combine the triptolide taught by Tao with the parthenolide taught by Hwang because Tao teaches that the selective inhibitory effect of EA and T2 extracts of *Tripterygium wilfordii* Hook F and its active component, triptolide, on expression of COX-2 but not COX-1, mRNA, provides desirable agents having antiinflammatory activity without the adverse effects associated with inhibition of COX-1 mediated PGE_2 production (see page 137, Column 2, lines 16-26). Further note that Hwang also teaches that parthenolide obtained from *Tanacetum parthenium* (feverfew) inhibited the expression of COX-2 and proinflammatory cytokines (TNFα and IL-1) in lipopolysaccharide (LPS) stimulated macrophages (see abstract). Moreover, it would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to combine the instant ingredients for their known benefit since each is well known in the art for their claimed purpose and for the following reasons. This rejection is based on the well established proposition of patent law that no invention resides in combining old ingredients of known properties where the results obtained thereby are no more than the additive effect of the ingredients, *In re Sussman*, 1943 C.D. 518. Applicants invention is predicated on an unexpected result, which typically involves synergism, an unpredictable phenomenon, highly dependent upon specific proportions and/or amounts of particular ingredients. Any mixture of the components embraced by the claims which does not exhibit an unexpected result (e.g., synergism) is therefore *ipso facto* unpatentable.

Accordingly, the instant claims, in the range of proportions where no unexpected results are observed, would have been obvious to one of ordinary skill having the above cited references before him.

From the teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Claims 1-25 are rejected under 35 U.S.C. 103(a) as being unpatentable over Tao et al. (U) and Hwang et al. (V) in view of Bath et al. (A), Petrus (B), Henderson et al. (C), Takamiya et al. (N, translation of foreign document provided herein), and Hesch (O).

Applicant's claimed invention of Claims 1-4, 6-9, 11-14, 16-19 and 21-24 was set forth above. Applicant further claims a composition, additionally containing one or more members selected from the group consisting of antioxidants, vitamins, minerals, proteins, fats, carbohydrates, glucosamine, chondroitin sulfate, and aminosugars.

The combined teachings of Tao and Hwang are set forth above. Tao and Hwang teach the claimed composition except for the instantly claimed ingredients. However, it would have been obvious to one of ordinary skill in the art to add one or more members selected from the group consisting of antioxidants, vitamins, minerals, proteins, fats, carbohydrates, glucosamine, chondroitin sulfate, and aminosugars to the composition taught by the combined teachings of Tao and Hwang to provide the claimed composition because at the time the invention was made the instantly claimed ingredients were known in the art for their beneficial therapeutic effects, as

evidenced by the teachings of Bath, Petrus, Henderson, Takamiya and Hesch. Firstly, Bath teaches a composition comprising glucosamine (e.g., glucosamine hydrochloride and glucosamine sulfate), collagen (protein), and a bioflavanol (e.g., antioxidants or bioflavanols extracted from grape seeds, pine bark or tumeric root, especially proanthocyanidins). The composition taught by Bath is used in the treatment of arthroses, such as primary and secondary osteoarthritis, and degenerative joint disease, in animals and humans. For instance, in a preferred treatment for larger animals, Bath teaches applying the composition as a top dressing twice a day to the animal's feed; and, in a preferred treatment for humans, dogs and cats, Bath teaches administering 1 to 4 tablets or capsules per day of the referenced composition. In specific Examples I-V, Bath shows that the composition further comprises vitamins (e.g., vitamin C and vitamin E), and minerals (e.g., manganese, zinc, and selenium). Secondly, Petrus teaches a composition comprising a nitric synthase inhibitor and aminosugars, which is used in treating arthritis, repairing articular joint surfaces and relieving symptoms associated with arthritis in animals and humans. In Column 6, lines 44-67, Petrus teaches that the composition further comprises a zinc salt. In Column 7, lines 52-62, Petrus also teaches that the referenced composition further comprises additional ingredients to promote the development and maintenance of cartilage, e.g., vitamins, minerals, glycosaminoglycans, and antioxidants, etc. Thirdly, Henderson teaches a composition comprising S-Adenosylmethionine (SAM), and either aminosugar and salts thereof (e.g., glucosamine) or glycosaminoglycans (e.g., chondroitin salts), which is used for the protection, treatment and repair and for reducing the inflammation of connective tissue in mammals. The

composition taught by Henderson may further comprise manganese and vitamins (see Column 9, lines 54-61). Fourthly, Takamiya teaches a composition comprising lactosucrose, calcium, chondroitin sulfate and vitamin D, which is orally administered to animals and humans in the treatment and/or prevention of osteoporosis (see page 2 of translation at [0011]-[0012]). Finally, Hesch teaches a composition comprising fats and carbohydrates, 50g of protein, and 100-2000 mg of calcium as a salt of a physiologically acceptable acid, and 1.25-15 micro-g of vitamin D, which is used for prevention of post-menopausal osteoporosis. At the time the invention was made, one of ordinary skill in the art would have been motivated and one would have had a reasonable expectation of success to add any of the instantly claimed ingredients to the composition taught by the combined teachings of Tao and Hwang to provide the claimed invention because in Column 8, lines 13-46, Bath teaches that the ingredients of his composition are required for effective joint supplement and repair therapy for the treatment of arthroses; Petrus teaches that the nitric oxide synthase inhibitor reduces the level of nitric oxide (the free radical believed responsible for the degradation of articular cartilage), amino sugars are the building blocks of articular cartilage and have inflammatory actions, and zinc regulates bone metabolism by stimulating bone formation and mineralization and an inhibitory effect on bone resorption; in Column 10, lines 9 to Column 11, lines 1-5, Henderson teaches that SAM, glucosamine and chondroitin salts stimulate the synthesis of collagen and glycosaminoglycans or mucopolysaccharides (GAGs), including hyaluronic acid, thereby providing a natural tissue repair function; Takamiya teaches that the ingredients of the referenced bone enhancement promoter are

useful in preventing and treating osteoporosis, and improve bone-salt deposition and contribute to bone enhancement by increasing the concentration of calcium in bone; and, Hesch teaches that the ingredients of the referenced composition have a synergistic effect, and that the composition is a low-calorie food which can be used at a stage at which bone metabolism has not yet led to pronounced loss of bone material. Moreover, it would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to combine the instant ingredients for their known benefit since each is well known in the art for their claimed purpose and for the following reasons. This rejection is based on the well established proposition of patent law that no invention resides in combining old ingredients of known properties where the results obtained thereby are no more than the additive effect of the ingredients, *In re Sussman*, 1943 C.D. 518. Applicants invention is predicated on an unexpected result, which typically involves synergism, an unpredictable phenomenon, highly dependent upon specific proportions and/or amounts of particular ingredients. Any mixture of the components embraced by the claims which does not exhibit an unexpected result (e.g., synergism) is therefore *ipso facto* unpatentable.

Accordingly, the instant claims, in the range of proportions where no unexpected results are observed, would have been obvious to one of ordinary skill having the above cited references before him.

From the teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at

the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Double Patenting

5. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

6. Claims 1-25 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-3, 6-14, 16-23, 25-32 and 34-38 of copending Application No. 09/919,510. Although the conflicting claims are not

identical, they are not patentably distinct from each other because the actual ingredients and resulting product(s) appear to be identical or essentially the same, and the functional beneficial effects of the ingredients used in the claim-designated methods are the same.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

7. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Michele Flood whose telephone number is (703) 308-9432. The examiner can normally be reached on Monday through Friday from 7:15 am to 3:45 pm. Any inquiry of a general nature or relating to the status of this application should be directed to the Group 1600 receptionist whose telephone number is (703) 308-0196 or the Supervisory Patent Examiner, Brenda Brumback whose telephone number is (703) 306-3220.

Michele C. Flood

MICHELE FLOOD
PATENT EXAMINER

MCF

April 28, 2003